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ORIGINAL ARTICLE

Comparison of 64-slice multi-detector computed tomography coronary angiography between asymptomatic, type 2 diabetes mellitus and impaired glucose tolerance patients

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Summary
Background: Cardiovascular disease is the most frequent cause of death and disability for diabetic patients, and patients with diabetes are more likely to have silent ischemia. Multi-detector computed tomography (MDCT) allows non-invasive assessment of coronary artery stenosis and plaque properties. In this study, we investigated whether 64-slice MDCT can non-invasively identify significant coronary artery stenosis in asymptomatic, type 2 diabetes mellitus (T2DM) and impaired glucose tolerance (IGT) patients.
Methods and results: The study population consisted of 154 consecutive asymptomatic patients [IGT ($n = 93$), T2DM ($n = 61$)]. All patients underwent contrast-enhanced 64-slice MDCT. The number of diseased coronary segments was classified as showing obstructive (≥50% luminal narrowing) disease or not. Significant coronary stenosis was detected in 43 (27.9%) of 154 enrolled patients. Patients with T2DM showed significantly more coronary stenosis than patients with IGT (41% vs. 19.4%; $p < 0.01$). Twenty-three patients [14.9%; IGT ($n = 9$), T2DM ($n = 14$)] underwent percutaneous coronary intervention (PCI) for severe stenosis. Patients with T2DM showed significantly more calcified plaque than IGT (47.5% vs. 29%; $p < 0.05$), but not significantly more soft plaque (19.7% vs. 15.1%; ns), or significantly different remodeling index (1.05 ± 0.18 vs. 1.04 ± 0.21; ns), respectively.

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Conclusions: 64-Slice MDCT can non-invasively identify significant coronary artery stenosis in asymptomatic, T2DM and IGT patients.

Introduction

The detection of sub-clinical coronary artery disease (CAD) before the development of life-threatening cardiac complications has great potential clinical relevance. Considerable discussion and debate are ongoing regarding the value of non-invasive screening for non-critical coronary atherosclerosis or silent ischemia secondary to flow-limiting stenosis in asymptomatic, type 2 diabetes patients.

Type 2 diabetes mellitus (T2DM) is becoming increasingly prevalent and is considered to increase the risk of heart disease by two to four times. Accordingly, 50% of deaths among diabetics in industrialized countries are due to heart disease. This proportion is declining, but more slowly than the equivalent for the general population [1]. CAD progresses relatively rapidly in diabetic patients, who, particularly in the setting of autonomic neuropathy, have impaired angina recognition and may often dismiss prior symptoms of myocardial ischemia [2,3]. Atypical symptoms can also prevent recognition by caregivers and be a cause of treatment delay [2]. Many diabetics with CAD do not develop any symptoms at all prior to an acute myocardial infarction; in fact, 22—39% develop silent myocardial ischemia [4,5]. Impaired glucose tolerance (IGT) is also a significant risk factor for CAD and a strong predictor of death from cardiovascular causes. Multi-detector computed tomography (MDCT) allows non-invasive assessment of coronary artery stenosis [6,7]. Recent advances in MDCT, especially in 64-slice MDCT, have dramatically improved spatial and temporal resolution. These advances have brought us not only visualization of the coronary artery lumen, but also assessment of plaque properties, i.e. hypodense plaque and plaque remodeling [8,9].

In this study, we investigated whether 64-slice MDCT can non-invasively identify significant coronary artery stenosis in patients with asymptomatic T2DM and IGT patients.

Methods

Patients

Our patient population was drawn from 154 consecutive, asymptomatic diabetic patients who were admitted to Sassa Medical Clinic from December 2005 to September 2007 for the evaluation of ischemic heart disease by 64-slice MDCT. All patients had another coronary risk factor of either hypertension or dyslipidemia. First, all patients underwent contrast-enhanced 64-slice MDCT. Thirty-five patients underwent invasive coronary angiography due to severe coronary stenosis, which was defined as a diameter reduction of >75%. Intravascular ultrasound (IVUS) was performed in all patients. The definition of DM was based on the cut-off point of fasting plasma glucose (FPG) of $\geq$126 mg/dl (7.0 mmol/L) or 75 g oral glucose challenge (2-h plasma glucose) of $\geq$200 mg/dl (11.1 mmol/L). The definition of IGT was based on the cut-off point of FPG of <126 mg/dl (7.0 mmol/L) and 75 g oral glucose challenge (2-h plasma glucose) was 140—199 mg/dl. No patients presented with any anginal equivalent symptoms. Patients who presented with ischemic echocardiographic (ECG) changes (n = 5), congestive heart failure (n = 3), non-adequate MDCT image due to heavily calcified lesions (n = 6), and arrhythmia (n = 4) were excluded.

This study complied with the Declaration of Helsinki. The protocol for the study was approved by the Ethics Committee of Osaka Ekisaikai Hospital. Written informed consent was obtained from all participants prior to MDCT.

Scan protocol of 64-slice MDCT

64-Slice MDCT data were acquired using a SOMATOM Sensation 64 cardiac (Siemens Medical Solutions, Forchheim, Germany). All patients with a heart rate of >70 bpm received β blocker (50 mg oral metoprolol) before the CT scan. A bolus of 65 ml of contrast media (Omnipaque350, Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan) was injected intravenously at a flow rate of 3.5—4.5 ml/s, followed by a 30 ml saline injection at the same flow rate.

Scans were obtained with a collimation of 0.66 mm with dual focus spots per detector row, a table feed of 11.6 mm/rotation, a tube current of 750—850 mA depending on patient body weight, a tube voltage of 120 kV, and a gantry rotation speed of 330 ms. An estimated mean effective radiation dose was approximately 13—20 mSv.

Image analysis of the coronary arteries by 64-slice MDCT

The analysis of 64-slice MDCT image data was performed by a single experienced reader. Image reconstruction was retrospectively gated to the ECG between 55 and 90% of the RR interval (every 5% increments). To acquire images of the best quality, additional reconstructions were performed at 2% of the RR interval before and after that phase following detection of minimum motion artifact. Overlapping trans-axial images were reconstructed using a medium sharp convolution kernel (B30f) with an image matrix of 512×512 pixels, slice thickness of 0.75 mm, and an increment of 0.3 mm using an ECG-gated one-segment scan algorithm with a resulting temporal resolution of 165 ms in the center of rotation. All main coronary arteries and large (>2 mm) side branches were evaluated irrespective of image quality. Maximum intensity projections were used to identify coronary lesions, and multi-planar reconstructions in two orthogonal longitudinal axes across the coronary lumen were utilized to classify lesions with significant stenosis, which was defined as a diameter reduction of >50%. Outer vessel area and arterial remodeling index were assessed by cross-sectional images. The arterial remodeling index was defined as the ratio of the outer vessel area at the site of maximal luminal narrowing and the mean of the proximal and distal reference sites. Soft plaque was defined as plaque showing CT attenuation values less than 50 Hounsfield units. Calcified plaque was defined as plaque showing CT attenuation values more than 130 Hounsfield units [9].

Invasive coronary angiography and IVUS imaging protocol

In 35 patients, coronary angiography was performed using a 6F Judkins-type catheter via the femoral or the radial approach. All patients received an intravenous bolus injection of 3000 IU of heparin and intracoronary isosorbide dinitrate (2 mg) before angiography. Coronary angiograms were reviewed separately by an independent observer, unfamiliar with the 64-slice MDCT findings.

After completion of diagnostic coronary angiography, and before any intervention, all patients were evaluated with IVUS. The IVUS catheter (2.9 F Atlantis, 40 MHz, Boston Scientific Corporation/SCIMED, Maple Grove, MN, USA) was carefully advanced distal to the lesion under fluoroscopic guidance.

The images were digitized and analyzed with commercially available software for longitudinal reconstructive IVUS image analysis (Netra IVUS, ScImage Inc., Los Altos, CA, USA). While pulling back the catheter, a contrast medium suitable for IVUS imaging was manually infused [10], and the lesion was carefully observed.

IVUS image analysis and intervention indication

IVUS images were interpreted by two independent, experienced observers unfamiliar with the 64-MDCT data. Evaluation of 2D lesion morphology and other measurements during IVUS was performed according to the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS) [11]. The minimum lumen area (MLA) of the culprit lesion was also measured. If the cases were determined to have an IVUS MLA of <4 mm^2, percutaneous coronary intervention (PCI) was performed.

Statistical analysis

Statistical analysis was performed using StatView 5.0J (Abacus Concept, Inc.). Results are expressed as mean value $\pm$ S.D. for continuous variables. Qualitative data are presented as numbers (%). Continuous variables have been compared using the paired *t*-test, and categorical data have been compared using the chi-square test with Fisher's exact test. A p value < 0.05 was considered statistically significant.

Results

Patient characteristics

MDCT was performed in all patients without any serious complications. Patient characteristics are summarized in Table 1. Patients with T2DM showed significantly higher serum levels of glycated hemoglobin (HbA1c) than patients with IGT (7.1 ± 1.1% vs. 5.5 ± 0.5%; $p < 0.01$). Of the 35 coronary angiographies, 23 cases were determined to have an IVUS MLA <4 mm^2 and PCI was performed. All 23 patients successfully underwent PCI. A higher number of T2DM patients underwent PCI compared to the IGT group [14 (23%) vs. 9 (9.7%); $p < 0.05$].

MDCT results

MDCT results are summarized in Table 2. Significant coronary stenosis was detected in 43 (27.9%) of

Table 1 Baseline patient characteristics

	Overall ($n = 154$)	IGT ($n = 93$)	T2DM ($n = 61$)
Age (years)	67 ± 8	68 ± 8	66 ± 9
Male gender	77 (50)	43 (46.2)	34 (55.7)
Number of risk factor			
Hypertension	118 (76.6)	75 (80.6)	43 (70.5)
Smoking	30 (19.5)	18 (19.4)	12 (19.7)
Dyslipidemia	57 (37)	40 (43)	17 (27.9)
Body mass index (kg/m^2)	24.6 ± 3.8	24.4 ± 3.7	24.7 ± 3.9
Performed PCI	23 (14.9)	9 (9.7)	14* (23)
HbA1c (%)	6.1 ± 1.1	5.5 ± 0.5	$7.1^{\dagger} \pm 1.1$
Current IGT/DM treatment			
SU	53 (34.4)	15 (16.1)	38 (62.3)
αGI	53 (34.4)	25 (26.9)	28 (45.9)
BG	16 (10.4)	6 (6.5)	10 (16.4)
PPARγ	18 (11.7)	8 (8.6)	10 (16.4)
Insulin	10 (6.5)	0 (0)	10 (16.4)
Known IGT/DM duration (years)	5.9 ± 4.7	4.2 ± 3	8.4 ± 5.6

Data are *n* (%), or mean ± S.D. *$p < 0.05$ vs. IGT; $^{\dagger}p < 0.01$ vs. IGT. IGT: impaired glucose tolerance; T2DM: type 2 diabetes mellitus; SU: sulfonylurea agent; αGI: alpha-glucosidase inhibitor; BG: biguanide agent; PPARγ: peroxisome proliferator-activated receptor gamma agonist.

154 enrolled patients. Patients with T2DM showed significantly more coronary stenosis than patients with IGT [25 (41%) vs. 18 (19.4%); $p < 0.01$]. Overall, 26 patients had single vessel disease (60.5%) and 17 patients had multi-vessel disease (39.5%). Patients with T2DM showed significantly more calcified plaque than patients with IGT [29 (47.5%) vs. 27 (29%); $p < 0.05$], but no significant difference for soft plaque [12 (19.7%) vs. 14 (15.1%); ns] or remodeling index (1.05 ± 0.18 vs. 1.04 ± 0.21; ns).

Fig. 1 shows an example of a typical case involving severe stenosis from an asymptomatic patient.

Characteristics of patients with and without PCI

In patients with and without PCI, there were no differences in age, gender, hypertension, smoking, dyslipidemia, body mass index, and serum level of HbA1c. Furthermore, there were no differences in the rate of drug treatment including sulfonylurea. MDCT findings of both groups are summarized in Table 3. Frequency of calcified lesions in the PCI group was significantly higher than those of the non-PCI group [13 (56.5%) vs. 43 (32.8%); $p < 0.05$]. The number of soft plaque lesions in the PCI group was higher than those of the non-PCI group [8 (34.8%) vs. 18 (13.7%); $p < 0.05$] and remodeling index (1.07 ± 0.16 vs. 1.02 ± 0.12; $p < 0.01$).

Discussion

Our study emphasizes the effectiveness of selectively using MDCT to identify individuals with CAD who may require more intensive therapy with either anti-ischemic or plaque-stabilizing medications and/or coronary revascularization.

Table 2 64-Slice MDCT results

	Overall ($n = 154$)	IGT ($n = 93$)	T2DM ($n = 61$)
Significant stenosis	43 (27.9)	18 (19.4)	$25^{\dagger}$ (41)
Single vessel disease	26 (60.5)	11 (61.1)	15* (60)
Multi-vessel disease	17 (39.5)	7 (38.9)	10 (40)
Calcium plaque	56 (36.4)	27 (29)	29* (47.5)
Soft plaque	26 (16.9)	14 (15.1)	12 (19.7)
Remodeling index	1.04 ± 0.17	1.04 ± 0.21	1.05 ± 0.18

Data are *n* (%), or mean ± S.D. *$p < 0.05$ vs. IGT; $^{\dagger}p < 0.01$ vs. IGT. Abbreviations shown as in Table 1.

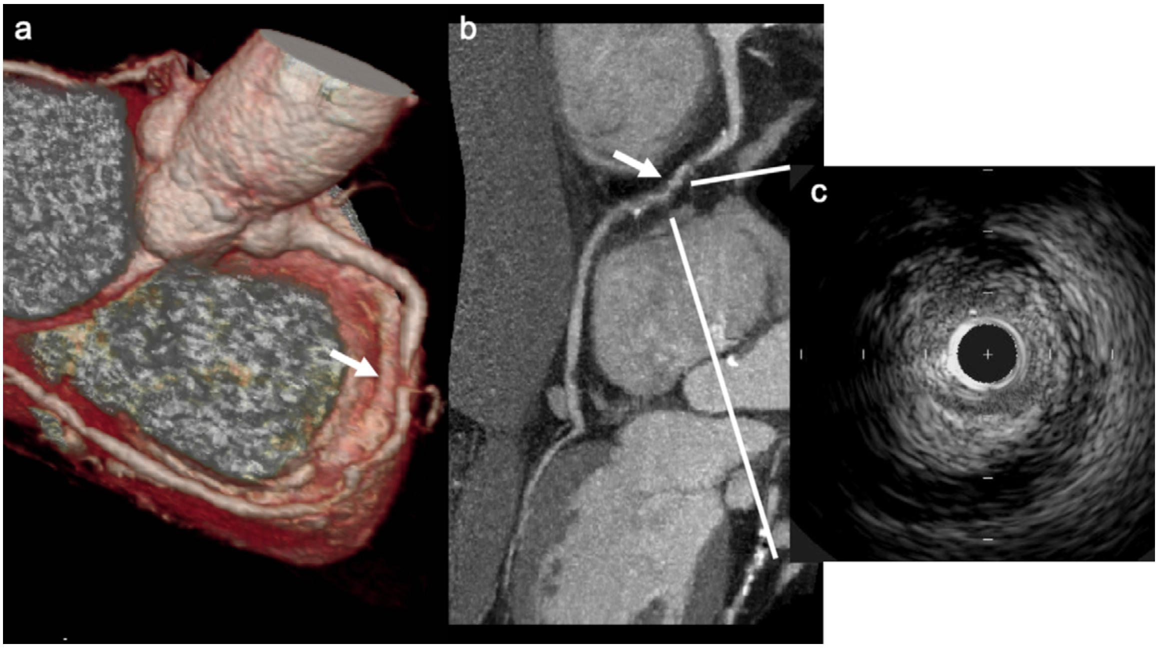

Figure 1 A patient with asymptomatic single vessel disease. Severe stenosis is observed at mid-portion of right coronary artery. (a) Volume rendering image. (b) Multi-planar reconstructions (MPR) image. (c) Intravascular ultrasound (IVUS) image of the lesion location.

The American Diabetes Association recommends cardiac testing in symptomatic patients with T2DM [12]. In non-diabetics, exercise ECG is a common non-invasive test for initially detecting CAD. However, diabetics are less likely to be able to perform an exercise test and are also more likely to have silent myocardial ischemia, which exercise ECG detects less accurately than other modalities [13]. Conversely, coronary MDCT has a clear role in detecting CAD in diabetics, and is now a widely

Table 3 Characteristics of patients with and without PCI

	With PCI ($n=23$)	Without PCI ($n=131$)
Age (years)	66 ± 8	67 ± 8
Male gender	12 (52.2)	65 (49.6)
Number of risk factor		
Hypertension	18 (78.3)	100 (76.3)
Smoking	4 (17.4)	26 (19.8)
Dyslipidemia	14 (60.9)	43 (32.8)
Body mass index (kg/m^2)	26.0 ± 4.1	24.4 ± 3.7
HbA1c (%)	6.4 ± 1.2	6.1 ± 1.1
Current IGT/DM treatment		
SU	9 (39.1)	44 (33.6)
αGI	10 (43.5)	43 (32.8)
BG	1 (4.3)	15 (11.5)
PPARγ	2 (8.7)	16 (12.2)
Insulin	3 (13)	7 (5.3)
Known IGT/DM duration (years)	7.4 ± 4.5	5.6 ± 4.7
MDCT calcium; number of lesion	13* (56.5)	43 (32.8)
MDCT soft plaque; number of lesion	8* (34.8)	18 (13.7)
MDCT remodeling index	$1.07 \pm 0.16^{\dagger}$	1.02 ± 0.12

Data are n (%), or mean ± S.D. *$p < 0.05$ vs. without PCI; $^{\dagger}p < 0.01$ vs. without PCI. Abbreviations shown as in Table 1. MDCT: multi-detector computed tomography.

available method for directly assessing coronary stenosis and coronary plaque, irrespective of symptoms [14,7,8,15,16].

It is widely believed that acute coronary syndrome is mainly caused by plaque rupture and secondary thrombus formation. Previous results from post-mortem studies have suggested that plaque rupture occurs most frequently at the point where the fibrous cap is thinnest and most heavily infiltrated by macrophage foam cells, a point that is most often found in the shoulder of eccentric plaques [17]. Our study results indicated soft plaque was detected in 16.9%, and as this strongly indicates the likelihood of being unstable plaque, it is necessary for patients with DM and hyperlipidemia to be considered for more aggressive treatment methods. 64-Slice MDCT is not only able to determine the level of stenosis, but also evaluate this type of unstable plaque.

IGT is also a significant risk factor for CAD and a strong predictor of death from cardiovascular causes. However, the benefits of treating IGT have only been recently evaluated. In the collaborative analysis of diagnostic criteria in Europe (DECODE) study, a project pooling data from over 22,000 individuals from 10 European population-based studies, individuals with IGT had a multivariate-adjusted hazard ratio of 1.34 [95% confidence interval (95% CI): 1.14—1.57] of death from CAD compared with those with normal glucose tolerance [18]. As per the results of our study, nine cases (9.7%) in the IGT group required PCI, and there was no significance in soft plaque (that could be considered unstable plaque) or positive remodeling when compared to the DM group. This suggests the importance of managing IGT patients.

Study limitations

There can be said to be a number of limitations associated with the present study. The number of the study population was relatively small. Calcium deposits deeply affected the reading of MDCT images. We excluded patients with heavily calcified plaque from the original population, which could have affected the accuracy of detection of different plaque types. MDCT is still associated with an elevated radiation dose, and the administration of contrast media is also required. Finally, the presence of ischemia cannot be detected with MDCT. Using IVUS, patients with an MLA < 4.00 mm^2 were considered to be ischemic and PCI was performed. This is consistent with the report by Nishioka et al. [19] that coincides well with stress myocardial scintigraphy.

Conflict of interest

None declared.

References

[1] Giri S, Shaw LJ, Murthy DR, Travin MI, Miller DD, Hachamovitch R, et al. Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease. Circulation 2002;105:32—40.

[2] Grundy SM, Howard B, Smith Jr S, Eckel R, Redberg R, Bonow RO. Prevention Conference VI: Diabetes and Cardiovascular Disease: executive summary: conference proceeding for healthcare professionals from a special writing group of the American Heart Association. Circulation 2002;105: 2231—9.

[3] Di Carli MF, Hachamovitch R. Should we screen for occult coronary artery disease among asymptomatic patients with diabetes? J Am Coll Cardiol 2005;45:50—3.

[4] Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, et al. Detection of ischemia in asymptomatic diabetics investigators. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. Diabetes Care 2004;27:1954—61.

[5] Zellweger MJ, Hachamovitch R, Kang X, Hayes SW, Friedman JD, Germano G, et al. Prognostic relevance of symptoms versus objective evidence of coronary artery disease in diabetic patients. Eur Heart J 2004;25:543—50.

[6] Achenbach S, Ulzheimer S, Baum U, Kachelriess M, Ropers D, Gisele T, et al. Noninvasive coronary angiography by retrospectively ECG-gated multislice spiral CT. Circulation 2000;102:2823—8.

[7] Hoffmann U, Moselewski F, Cury RC, Ferencik M, Jang IK, Diaz LJ, et al. Predictive value of 16-slice multidetector spiral computed tomography to detect significant obstructive coronary artery disease in patients at high risk for coronary artery disease: patient-versus segment-based analysis. Circulation 2004;110:2638—43.

[8] Raff GL, Gallagher MJ, O'Neill WW, Goldstein JA. Diagnostic accuracy of noninvasive coronary angiography using 64-slice spiral computed tomography. J Am Coll Cardiol 2005;46:552—7.

[9] Leber AW, Knez A, von Ziegler F, Becker A, Nikolaou K, Paul S, et al. Quantification of obstructive and nonobstructive coronary lesions by 64-slice computed tomography: a comparative study with quantitative coronary angiography and intravascular ultrasound. J Am Coll Cardiol 2005;46:147—54.

[10] Tanaka A, Kawarabayashi T, Taguchi H, Nishibori Y, Sakamoto T, Nishida Y, et al. Use of pre-intervention intravascular ultrasound in patients with acute myocardial infarction. Am J Cardiol 2002;89:257—61.

[11] Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, et al. American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2001;37:1478—92.

[12] Consensus development conference on the diagnosis of coronary heart disease in people with diabetes: 10—11 February 1998, Miami, Florida. American Diabetes Association. Diabetes Care 1998;21:1551—9.

[13] Bax JJ, van der Wall. Assessment of coronary artery disease in patients with asymptomatic diabetes. Eur Heart J 2006;27:631—2.
[14] Achenbach S, Ulzheimer S, Baum U, Kachelriess M, Ropers D, Giesler T, et al. Noninvasive coronary angiography by retrospectively ECG-gated multislice spiral CT. Circulation 2000;102:2823—8.
[15] Lin F, Shaw LJ, Berman DS, Callister TQ, Weinsaft JW, Wong FJ, et al. Multidetector computed tomography coronary artery plaque predictors of stress-induced myocardial ischemia by SPECT. Atherosclerosis 2008;197:700—9.
[16] Hoffmann U, Nagurney JT, Moselewski F, Pena A, Ferencik M, Chae CU, et al. Coronary multidetector computed tomography in the assessment of patients with acute chest pain. Circulation 2006;114:2251—60.
[17] Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation 1995;92:657—71.
[18] DECODE Study Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med 2001;161:397—404.
[19] Nishioka T, Amanullah AM, Luo H, Berglund H, Kim CJ, Nagai T, et al. Clinical validation of intravascular ultrasound imaging for assessment of coronary stenosis severity: comparison with stress myocardial perfusion imaging. J Am Coll Cardiol 1999;33:1870—8.